PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
MH50016		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2003/000277	20.02.2003	22.02.2002
International Patent Classification (IPC) or national classification and IPC		
C12Q 1/68, G01N 33/53		
Applicant		
Avaris AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.09.2003	25.05.2004
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International Application No.
PCT/SE2003/000277

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-15 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* 16-18 received by this Authority on 01.04.2004
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-13 (partially)

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-13 (part.) are so unclear that no meaningful opinion could be formed *(specify)*:

A complete search of the entire scope of the claims was not conducted at the search stage due to the wording of the original claims. The search was limited to what is revealed in the examples and to some extent to the general features of the invention. This opinion covers the part of the scope of claims 1-13 that was stated to have been searched in the International Search Report. For further details, see also Box V.

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☒ the claims, or said claims Nos. 1-13 (partially) are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-13 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box III

The terms "molecules of interest", "biomolecular complexes comprising at least two functional elements", "attached to a target molecule or area", "through binding elements", "nucleic acid polymer having a predetermined physical property", "functional entities", "binding entities" , "reacting ... with ..." used in e.g. claims 1, 5 and 6 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear to the extent that it is impossible to give a meaningful opinion valid over the whole of the scope of the claims (Article 6 PCT).

Present claims 4 and 9-13 relate to a product/compound defined by reference to a desirable characteristic or property, drug candidates, combinatorial libraries and drug delivery vectors ("reach through" claims). The claims cover all products/ compounds/ libraries/ vectors having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful evaluation over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lacks clarity (Article 6 PCT). An attempt is made to define the product/compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful evaluation of novelty, inventive step and industrial applicability over the whole of the claimed scope impossible.

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	4	YES
	Claims	1-3, 5-8	NO
Inventive step (IS)	Claims	4	YES
	Claims	1-3, 5-8	NO
Industrial applicability (IA)	Claims	4-8	YES
	Claims	1-3	NO

2. Citations and explanations (Rule 70.7)

Claims 1-3 have been amended and now relate to a method for the study of inter-molecular interactions. The lack of clarity and conciseness pointed at have not been eliminated by these amendments. Furthermore, claim 1 lacks information concerning the different steps of the method needed to make it industrially applicable e.g. no "functional entity" is defined, no measurement method is indicated and no "physical property" is revealed, nor the necessary cooperation of these to produce a useful result. At least the last two items are also absent in claims 2 and 3. Therefore, claims 1-3 are considered to lack clarity and conciseness even to the extent that industrial applicability cannot be acknowledged.

To the extent the claims refer to assays revealing the distances between receptors with aid of PNA constructs (as revealed in the examples), novelty and inventive step might be acknowledged. The use of two target DNA sequences separated by a nucleotide linker can provide for the right distance between the target sequences and, consequently, between ligands bound to these sequences. These constructs are used to simultaneously present RGD, TAT and BULKY ligand combinations or single or multiple "entities" e.g. Btk, to receptors on cells and to evaluate the effects on binding strength of such combinations.

Claims 5 and 6-7 refer to methods for the production of a biomolecular complex. The methods essentially comprise standard methods (forming stock solutions, reacting functional and binding entities and forming complexes) in addition to the vague definitions discussed with regard to claims 1-3. The methods seem not to embrace the gist of the invention (i.e. they do not reveal the combination of structural features in the complex that creates a given measurable response when the two "functional entities" are in cooperation with the "target".

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Claim 8 restricts the binding entities to PNA without stating the other components of the complex or the detection method.

In conclusion the vague wording of the claims still makes it impossible to evaluate the inventive step over the whole breath of the claims. Novelty may be at hand but the entire scope of the claims is such as to go far beyond what was covered in the International Search. Consequently, novelty and/or inventive step cannot be acknowledged for the whole scope of claims 1-3 and 5-8.

Cited documents referred to in the Search Report and written opinion:
D1 WO9416108
D2 WO9118117
D3 US6017707
D4 WO9807845
Doc. D1 (see e.g. fig 7 and p 41 lines 19-23) reveals a biomolecular complex with two functional elements (biotin) each of which are linked to separate binding elements (polynucleotides), each binding element selectively binding to a target area polynucleotide(s) through hybridisation. Two target areas are connected through a linker sequence.
Doc. D2 fig. 8 (see also text to figures on p 22-23) displays a biomolecular complex with two different functional elements (paramagnetic particle and "hairpin" structure) binding to two target areas through separate binding elements. The target areas are connected through linker sequences.
Doc. D3, fig 6 shows a complex comprising two different functional elements (antibody and "tracer"; column 9 lines 9-27) bound to separate target areas through separate binding elements. Binding elements and target areas bind each other selectively through hybridization and several different target areas are connected through a polymer that is considered to function as a linker.
Doc. D4 (see pages 8-28 and fig IIa) refers to constructs for in vivo testing of interactions between two "functional elements" (bait and prey fusion proteins).

These documents are considered to represent the state of the art.

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Claims

1. A method for the study of inter-molecular interactions under physiological or near-physiological conditions, **characterized** in that

   - the molecules of interest, being the same or different, are inserted as functional entities (FE) in a biomolecular complex comprising at least two functional elements (FE_1, FE_2) each attached to a target molecule or area (T) through binding elements (BE), wherein each FE is attached to a specific BE, said BE being a nucleotide sequence and the target molecule or area comprising the corresponding target sequence, and the target molecules or areas being separated from each other by a first linker or spacer (L) and an optional second linker (l), said linkers being nucleic acid polymers having a pre-determined physical property; and

   - the orientation and distance between the molecules being varied by varying at least one of the first and second linker (L, l).

2. The method according to claim 1, wherein receptors are screened with respect to their involvement in the internalisation of substances in a cell.

3. The method according to claim 2, wherein the cells are chosen among eukaryotic and prokaryotic cells, and the functional elements substituted by ligands presumed to interact with said receptors.

4. Drug candidates identified using the method according to any one of claims 1 - 3.

5. Method for the production of a biomolecular complex comprising at least two functional elements (FE_1, FE_2) each attached to a target molecule or area (T) through binding elements (BE), wherein each FE is attached to a specific BE, said BE being a nucleotide sequence and the target molecule or area comprising the corresponding target sequence, and the target molecules or areas being separated from each other by a first linker or spacer (L) and an optional second linker (l), said linkers being nucleic acid polymer s having a pre-determined physical property; said method comprising the steps of

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a) forming a stock solution of a first functional entity,

b) forming a stock solution of a second functional entity,

c) forming separate stock solutions of at least two binding entities,

d) forming separate stock solutions of nucleic acid molecules as linker molecules, each solution containing a linker having a distinct physical property,

e) reacting said first functional entity with at least one binding entity,

f) reacting said second functional entity with at least one binding entity, other than the binding entity in e)

g) repeating steps e) and f) for each functional entity,

h) reacting each linker molecule with at least two target molecules / target areas, capable of specific binding to the binding entities of e) and f)

i) reacting each combination of functional entity and binding entity with each linker, and

j) repeating step h) in order to form a library of combinations of functional entities and linkers.

6. Method for the production of a biomolecular complex comprising at least two functional elements (FE_1, FE_2) each attached to a target molecule or area (T) through binding elements (BE), wherein each FE is attached to a specific BE, said BE being a nucleotide sequence and the target molecule or area comprising the corresponding target sequence, and the target molecules or areas being separated from each other by a first linker or spacer (L) and an optional second linker (l), said linkers being nucleic acid polymer s having a pre-determined physical property; said method comprising the steps of

i) synthesis of a molecular combination of a first functional entity and a first binding entity,

ii) synthesis of a molecular combination of said first functional entity and a second binding entity,

iii) synthesis of a molecular combination of a second functional entity and said first binding entity,

iv) synthesis of a molecular combination of a second functional entity and said second binding entity,

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optionally repeating steps i) – iv) for further functional entities and binding entities and forming stock solutions thereof,

v) synthesis of a nucleic acid molecule as a linker connecting a first and second target area, and.

vi) self-assembly of the molecular combinations of any one of step i) – iv) to the linker of step v) in the desired configuration by addition of these to said linker in solution.

7. Method according to any one of claims 5 - 6, wherein the linker molecule comprises a marker or label chosen among a reporter gene, a radioactive label, and a fluorescent label.

8. Method according to any one of claims 5 - 6, wherein the binding entities are PNA sequences.

9. A combinatorial library produced by the method according to any one of claims 5 - 6.

10. A combinatorial library according to claim 9, wherein the functional entities are chosen among a natural or synthetic peptide, a lipid, a glycoprotein, a receptor ligand, and a fraction of any of the preceding.

11. Drug delivery vectors produced using the method according to any one of claims 5 - 6.

12. Drug delivery vectors identified using a combinatorial library according to any one of claims 9 - 10.

13. Drug candidates identified using a combinatorial library according to any one of claims 9 - 10.
